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FULL LENGTH ARTICLE

Evaluation of aggressive heart rate reduction in patients with stable angina

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KEYWORDS

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Abstract *Background:* There is a strong correlation between heart rate and myocardial ischemia, cardiovascular diseases, and life expectancy in general; however, heart rate has been neglected as an important risk factor as well as a therapeutic opportunity.

Purpose: To investigate the effect of aggressive heart rate reduction ($50 \leqslant HR \leqslant 60$ bpm) on anti-ischemic and anti-anginal efficacy, left ventricular function, exercise tolerance and quality of life in patients with stable coronary artery disease with or without left ventricular dysfunction during 4 months.

Methods: A total of 159 patients presented with stable CAD without clinical heart failure symptoms were included in a open-label, non-comparative, prospective clinical study between June 2009 to February 2010 in King Abdul Aziz Specialist Hospital, Taif, KSA, Al Hayah National Hospital, Khamis Mushyt, KSA and Critical care department, Cairo University, Egypt. All included patients were, in addition to the ant ischemic treatment, subjected to aggressive heart rate control starting by beta blocker titrated to the maximum dose as tolerated, then Ivabradine added if the target heart rate is not achieved or rate control started by Ivabradine if beta blockers are contraindicated. Exercise treadmill test (ETT) to assess exercise capacity using time to 1 mm ST-segment depression in milliseconds, ejection fraction (EF) assessed by transthoracic echocardiography and frequency of angina

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attacks and the use of sublingual nitroglycerin per week during the last week were evaluated during a follow-up for 4 months. The patients were divided into two groups, group-I (patients achieved a resting heart rate between 50 and 60 bpm with heart rate reduction treatment) and group-II (patients with resting HR >60 bpm in spite of maximum treatment for heart rate reduction).

Results: The resting heart rate was significantly reduced from 77.98 ± 8.7 at baseline to 60.68 ± 4.34 bpm after 4 months of treatment, $P < 0.001$. The frequency of angina pectoris attacks had been significantly reduced from 2.14 ± 1.27 to 0.48 ± 0.58 attacks per week, $P < 0.001$ and the highest significant reduction was observed with group-I. Also, the frequency of use sublingual nitrate therapy was significantly reduced from 1.38 ± 1.1 tablet per week at the last week before the study to 0.12 ± 0.33 tablet per week during the last week after 4 months of treatment, $P < 0.001$ and the reduction was more significantly with group-I. Exercise treadmill test demonstrated statistically significant increase in the time to 1 mm ST-segment depression from 357.36 ± 66.73 at baseline to 387.96 ± 65.19 ms. after 4 months with $P < 0.001$. The degree of improvement was significantly higher for group-I (from 358.06 ± 68.81 at baseline to 391.71 ± 69.01 after 4 months with $P < 0.001$) than that of group-II (from 356.11 ± 64.8 at baseline to 381.27 ± 59.08 after 4 months with $P < 0.001$). Ejection fraction showed a statistically significant increase from 59.76 ± 6.86 at baseline to 61.04 ± 5.35 after 4 months with $P < 0.001$.

Conclusion: This study indicates that heart rate reduction has been associated with an improvement in quality of life in patients with stable coronary artery disease, presenting new opportunities for treatment.

1. Introduction

An increase in pulse rate is the simplest and most effective way to raise cardiac output in response to an increase in total oxygen requirement. The contraction cycle determines >90% of myocardial oxygen demand. Heart rate (HR) is, therefore, an important determinant of myocardial oxygen consumption. Other important modulators of oxygen consumption per beat are the inotropic state, or the velocity of contraction, and the developed wall tension. Resting HR varies between species and among healthy individuals, and has been shown to be an index of expected life span (Levine, 1997).

In the Göteborg multifactor primary prevention trial, which included healthy men during a follow-up period of 12 years, total mortality and, in particular, coronary mortality, were closely related to HR. There was a two- to threefold increase in mortality in subjects with a HR of >90 beats per minute (bpm) compared with those <60 bpm (Wilhelmsen et al., 1986). In another study of 7079 men, without ischemic heart disease and a follow-up period of 23 years, resting HR was an independent risk factor for sudden death (Jouven et al., 2001). Moreover, in the Framingham study, HR was directly related to total mortality, cardiovascular mortality, and coronary mortality (Gillman et al., 1993).

The relationship between HR and life expectancy is found, not only in humans, but also in other mammals; this relationship is so strong that the average total heart beats per lifetime is remarkably constant and has been calculated as 7.3×10. Clearly, increased HR shortens life but it is unknown if HR reduction in the healthy population prolongs life (Levine, 1997; Gillman et al., 1993).

In patients with coronary artery disease, high resting HR is a prognostic determinant of cardiovascular risk during and after an acute event (Hjalmarson et al., 1990). This is supported by studies in animals, demonstrating that elevated heart rate increases oxygen requirement and shortens the time to myocardial dysfunction and necrosis (Shell and Sobel, 1973). Conversely, reductions in HR confer protection of the ischemic myocardium (Kjekshus et al., 1981). The same relationship has been observed in patients with heart failure (Gillman et al., 1993).

Dyslipidemic inflammatory conditions and diabetes are associated with blunting of autonomic control, with enhanced sympathetic and reduced vagal influence on the sinus node in association with a higher cardiovascular risk in these conditions. Particular attention has, therefore, been paid to the importance of HR as a target for therapy (Sajadieh et al., 2004).

2. Aim of the work

The objectives of this study are to determine the effect of aggressive HR reduction ($50 \leqslant HR \leqslant 60$ bpm) on anti-ischemic and anti-anginal efficacy, left ventricular function, exercise tolerance and quality of life in patients with stable coronary artery disease with or without left ventricular dysfunction during 4 months.

3. Patients and methods

3.1. Design

The study between June 2009 to February 2010 in King Abdul Aziz Specialist Hospital, Taif, KSA, Al Hayah National Hospital, Khamis Mushyt, KSA and Critical care department, Cairo University, Egypt is a open-label, non-comparative, prospective clinical trial. The study included 159 patients presenting with stable coronary artery disease without clinical heart failure symptoms.

3.2. Ethics

The study protocol was approved by the local Ethics Committee. This study did not interfere with the current medical practice of the investigator. No invasive medical procedure is required by the protocol. The investigator can decide for any treatment that is for the best interest of his patients.

3.3. Selection of the population

3.3.1. Inclusion criteria

(1) Patients older than 18 years, (2) patients from either sex, (3) out-patients presenting with documented stable coronary artery disease with or without left ventricular dysfunction, (4) patients with stable angina >6 months since diagnosis and (5) resting HR >60 bpm.

Patients who were excluded from the present study included those who were younger than 18 years of age, presented with clinical heart failure, i.e. stage III or IV of the New York Heart Association (NYHA) classification, had unstable angina or MI <6 months, had Arrhythmia or associated condition or those who are pregnant or lactating.

3.3.1.1. Treatment. Step-by-step target driven strategy, upon investigator evaluation starting by β-blockers titrated to maximum dose as tolerated, then Ivabradine added if target HR is not achieved or one can start by Ivabradine if β-blockers are contraindicated. β-Blocker therapy was started in a daily dose of 25 mg atenolol or 2.5 mg bisoprolol daily. The dose was increased gradually during a follow up period of 2–4 weeks up to a maximum daily dose of 200 mg atenolol or 10 mg bisoprolol. Ivabradine was started in a dose of 5 mg, twice daily. The dose was increased gradually during a follow up period of 2–4 weeks up to a maximum dose of 7.5 mg, twice daily. A starting reduced dose of 2.5 mg, twice daily was recommended in patients with age >75 years, in addition to β-blocker if target HR is achieved or HR continuously <50 bpm during treatment.

3.3.1.2. Assessments

– Visit 1 (week 0): Inclusion visit

1. Patient demographics
2. Cardiovascular risk factors
3. History of cardiovascular events
4. Resting blood pressure and HR:

– Patients should be at rest in sitting position for 5 min
– Systolic and diastolic blood pressure are measured by a sphygmomanometer
– Resting HR is measured by physical palpation and counting for one minute
– Resting HR is then measured by an electrocardiogram.

5. Current cardiovascular treatments
6. Frequency of angina attacks and use of sub-lingual (SL) nitroglycerin per week during the last week.
7. Exercise treadmill test (ETT) to assess exercise capacity using time to 1 mm ST-segment depression in milliseconds
8. Ejection fraction (EF) by echocardiography: The echocardiography images were obtained using a transducer 3.5 MHz with 2D guided M-mode facilities. All patients were examined in the partial left lateral decubitus and were angled according to necessity to obtain optimal windows for optimal views according to the recommendations of the American Society of Echocardiography (Sahn et al., 1978). Patients with non optimum windows were excluded from the study. Images were obtained in the parasternal long axis, parasternal short axis (mid-level), apical two and four chamber views. Optimization was performed using harmonic imaging, gain, dynamic range, frequency, sector width and focus to improve signal-to-noise ratio and provide optimal endocardial definition and images were accepted for analysis according to the guide lines proposed by Gordon et al. (1983) when at least 80% of endocardium was seen. Left ventricular end diastolic dimension, left ventricular end systolic dimension and fraction shortening were assessed by parasternal long axes view with M-mode technique by placing the curser just below the tips of the anterior mitral valve leaflets cutting perpendicularly the right ventricle, basal interventricular septum and posterior wall. Left ventricular end diastolic volume, Left ventricular end systolic volume, FS and ejection fraction were assessed by apical four chamber and two chamber views with the modified Simpson's method (Weyman and Doty, 1982). This was performed at both end-diastole and systole. End-diastole was taken to coincide with the Q-wave on the electrocardiogram and end-systole was selected by identifying the frame with smallest LV cavity cross-sectional area in both apical views prior to mitral valve opening. The parameters were averaged from three consecutive measurements.

– Visit 2 (week 4): Follow-up visit 1

1. Resting blood pressure and HR: the same as inclusion visit
2. Current cardiovascular treatments
3. Frequency of angina episodes and use of SL nitrates during the last week

– Visit 3 (after 16 weeks): End of the study

1. Resting blood pressure and HR: the same as before
2. Current cardiovascular treatments
3. Frequency of angina episodes and use of SL nitrates per week
4. ETT using time to 1 mm ST-segment depression in milliseconds
5. EF by echocardiography

3.3.1.3. End-points

Primary end-points:

1. Resting HR reduction from baseline
2. Improvement in exercise tolerance parameter by ETT. Assessment is done for time to 1 mm ST-segment depression in milliseconds
3. Improvement in EF

Secondary end-points:

1. Decrease of angina episodes and use of SL nitrates
2. Mean change in blood pressure from week 0 to week 12
3. Evolution of the quality of life from week 0 to week 4 and week 12 by the frequency of angina episodes and use of SL nitrates

The primary and second end points were analyzed on all patients who are divided into two groups:

- Group-I: patients who achieved a resting HR between 50 and 60 bpm after 2–4 weeks of HR reduction treatment.
- Group-II: patients with resting HR >60 bpm in spite of maximum treatment for HR reduction.

4. The statistics

Data were collected and verified prior to analysis, statistical analyses were performed using SPSS software for windows, version 18.0 (SPSS Inc., Chicago IL, USA). Continuous data are presented as mean + SD or median and compared using student *t*-test. Differences in the occurrence of angina pectoris attacks and in the need for the use of sublingual nitrates were evaluated using the Wilcoxon signed rank test. Categorical variables were reported as absolute numbers (frequency percentages). A P value <0.05 was considered to be significant.

5. Results

5.1. Demographic and clinical data of the patients included

Out of 200 patients, only 159 patients completed the protocol of the study. Ninety nine (62.3%) were male and 60 (37.7%) were female, with mean age 56.7 ± 11.4 years. Forty one patients did not complete the study protocol because of non optimum echocardiographic window ($n = 14$), incompliance of the patient ($n = 9$), the fact that the patient was symptom free and the patient terminated his or her therapy independently ($n = 18$).

Mean systolic blood pressure was lowered from 137.04 ± 13.12 to 129.72 ± 6.62 mmHg ($P < 0.001$) between baseline and the fourth month of treatment with beta blocker ± other antihypertensive drugs. Also, mean diastolic blood pressure was lowered from 85.7 ± 8.73 to 80.44 ± 5.8 mmHg ($P < 0.001$).

Table 1 Demographic and clinical data of patients entered into the study.

Characteristics	Value
Age: (mean ± SD in years (Range))	56.7 ± 11.4 (39–77)
Male:Female sex (No. of patients ratio)	99:60 (1.65)
CCS classification (Campeau, 1976)	(No. of patients (%))
Geade I	45 (28.3%)
Geade II	59 (37.1%)
Geade III	47 (29.6%)
Geade IV	8 (5%)
Concomitant disease	
Hypertension	84 (52.8%)
Diabetes mellitus	69 (43.4%)
Dyslipedemia	93 (58.5%)
Cholesterol	55 (34.6%)
Triglyceride	3 (1.9%)
Mixed	35 (22%)
Family history	68 (42.7%)
Smoker	55 (34.6%)
Bronchial asthma	10 (6.3%)
Chronic obstructive air way disease	26 (16.3%)
Cerebrovascular disease	8 (5%)
Hyperthyroidism	3 (1.9%)

The Canadian Cardiovascular Society (CCS) classification of angina pectoris of the patients is given in Table 1 (Campeau, 1976).

Calcium channel blocker was given as adjunctive to control the hypertension and not used as line of rate control. Rate control achieved only by β-blocker ± Ivabradine (Table 2).

5.2. Heart rate and ECG parameters

The resting HR was significantly reduced from 77.98 ± 8.7 (65–102) at baseline to 60.68 ± 4.34 (54–74) bpm at the third visit after 4 months of treatment, P value <0.001 (Fig. 1). The magnitude of reduction of HR was significantly higher with group-I than the reduction of group-II (Table 3).

No relevant changes were observed in ECG parameters, for example, PR, QRS and QT_c periods. Marked physiological changes were only observed in R–R interval and in the uncorrected QT associated with the reduction of HR.

5.3. Angina pectoris and nitrate consumption

Out of the 159 patients, 147 (92.5%) patients had a minimum of one angina pectoris attack per week during the last week before the start of the study. At the follow-up after 4 months of anti-ischemic treatment including HR lowering drugs, the frequency of angina pectoris attacks had been significantly reduced.(2.14 ± 1.27 (0–5) to 0.48 ± 0.58 (0–2) attacks per

Table 2 Cardiovascular medications of patients included into the study.

	Time	Total (No. 159)	Group I (No. 96)	Group II (No. 63)
Long acting nitrates	W0	99	55	44
	W4	97	54	43
	W16	97	54	43
Anti platelet	W0	158	96	62
	W4	159	96	63
	W16	159	96	63
ACE-I	W0	38	24	14
	W4	45	25	20
	W16	45	25	20
AT-II antagonist	W0	49	29	20
	W4	49	29	20
	W16	49	29	20
CCB	W0	45	21	24
	W4	45	21	24
	W16	45	21	24
Statin	W0	95	60	35
	W4	105	63	42
	W16	105	63	42
β-blocker	W0	102	82	21
	W4	62	52	10
	W16	50	40	10
Ivabradine	W0	30	6	24
	W4	36	6	30
	W16	36	6	30
β-blocker + Ivabradine	W0	27	15	12
	W4	61	33	27
	W16	73	42	31

ACE-I, angiotensin converting enzyme inhibitor; CCB, calcium channel blocker; AT-II antagonist, angiotensin II antagonist; W, week.

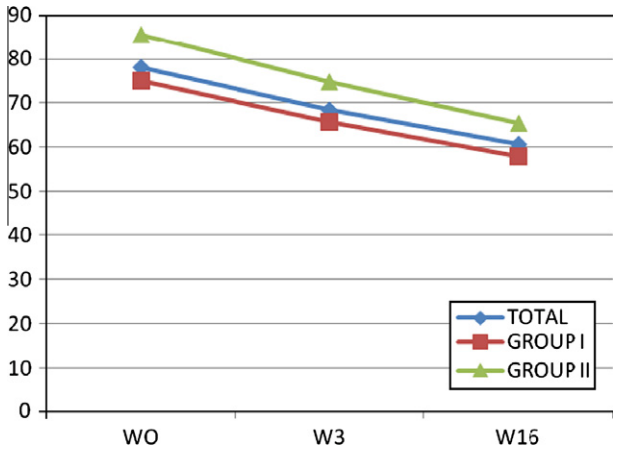

Figure 1 Heart rate trend of the patents.

week, $P < 0.001$). The highest significant reduction was observed with group I (0.28 ± 0.45 (0–1) attack per week).

Also, the frequency of use sublingual nitrate therapy was significantly reduced from 1.38 ± 1.1 (0–4) tablet per week at the last week before the study to 0.12 ± 0.33 (0–1) tablet per week during the last week after 4 months of treatment, $P < 0.001$. The reduction was more significantly with group-I 0.04 ± 0.17 tablet per week.

5.4. Exercise tolerance and EF

Our study revealed that exercise tolerance assessed by exercise treadmill test showed a statistically significant increase in the time to 1 mm ST-segment depression after 4 months of anti-ischemic treatment including rate control drugs from 357.36 ± 66.73 (236–466) at baseline to 387.96 ± 65.19 (269–487) ms. after 4 months with $P < 0.001$. The degree of improvement was significantly higher for group-I (from 358.06 ± 68.81 at baseline to 391.71 ± 69.01 after 4 months with $P < 0.001$) than that of group-II (from 356.11 ± 64.8 at baseline to 381.27 ± 59.08 after 4 months with $P < 0.001$).

Ejection fraction assessed by transthoracic echocardiography showed a statistically significant increase after 4 months of treatment (from 59.76 ± 6.86 at baseline to 61.04 ± 5.35 after 4 months with $P < 0.001$). The degree of increase was non significantly higher for group-I (from 59.96 ± 6.84 at baseline to 61.09 ± 5.03 after 4 months) than that of group-II (from 59.38 ± 7.07 at baseline to 60.94 ± 6.03 after 4 months).

6. Discussion

The rate of sinus rhythm, or HR, is one of the most easily measured basic physiological characteristics. Resting HR is known to be an independent risk factor associated with overall and cardiovascular mortality in the general population, as well as in patients with arterial hypertension, metabolic syndrome, and coronary artery disease. Therefore HR has attracted the growing attention of researchers because of its re-endorsed prognostic significance and new therapeutic opportunities for its control (Levine, 1997; Benetos et al., 1999; Hozawa et al., 2004).

For this reason, our study was conducted in order to determine the effect of aggressive HR reduction ($50 \leqslant HR \leqslant 60$ bpm) on anti-ischemic and anti-anginal efficacy, left ventricular function, exercise tolerance and quality of life in patients with stable coronary artery disease with or without left ventricular dysfunction during 4 months of follow-up.

We demonstrate that resting HR was significantly reduced from 77.98 ± 8.7 to 60.68 ± 4.34 bpm, $P < 0.001$ between baseline and the third visit after 4 months of anti ischemic treatment including HR lowering drugs. β-Blockers (except those with sympathomimetic effect) are used as first line pharmacologic treatment for heart rate reduction; the dose was adjusted to secure a resting HR ⩽60 bpm. In some patients, therapy with β-blocker was limited by side effects such as chronic asthma, obstructive airway disease, hypotension and non adequate response, preventing appropriate HR reduction, making the use of other rate lowering drug; sinus node inhibitor, as adjunctive or alternative treatment.

Sinus node inhibitor, Ivabradine, is a selective bradycardiac agent approved for clinical use in patients with stable angina. It reduces the firing rate of the pacemaker cells in the sinoatrial node at rest and exercise by blocking I_f ion channels on the

Table 3 Clinical outcome of patients included into the study.

	Time	Total	Group I	Group II	LSD at 0.05
HR	WO	77.98 ± 8.71	73.93 ± 6.99	85.16 ± 6.64	
	W16	60.68 ± 4.34	57.87 ± 1.69	65.66 ± 2.80	
	P value	<0.001	<0.001	<0.001	
Frequency of angina	WO	2.14 ± 1.27	1.87 ± 1.23	2.61 ± 1.24	0.37
	W16	0.48 ± 0.58	0.28 ± 0.45	0.83 ± 0.62	
	P value	<0.001	<0.001	<0.001	
Frequency of SLN	WO	1.38 ± 1.10	1.06 ± 0.94	1.94 ± 1.16	0.29
	W16	0.12 ± 0.32	0.03 ± 0.17	0.27 ± 0.46	
	P value	<0.001	<0.001	<0.001	
ETT (ms)	WO	357.36 ± 66.73	358.06 ± 68.81	356.11 ± 64.8	25.67
	W16	387.96 ± 65.19	391.71 ± 69.01	381.27 ± 59.08	
	P value	<0.001	<0.001	<0.001	
EF (%)	WO	59.76 ± 6.86	59.96 ± 6.84	59.38 ± 7.07	14.68
	W16	61.04 ± 5.35	61.09 ± 5.03	60.94 ± 6.03	
	P value	<0.001	0.032	0.003	

HR, heart rate; SLN, sublingual nitrate; ETT, Exercise treadmill test; EF, ejection fraction; W, week; LSD, least significant difference at $P = 0.05$.

cellular membrane and inhibiting the mixed Na/K inward diastolic current. The I_f current, activated by hyperpolarization and modulated by the autonomic nervous system, drives the slow diastolic depolarization, which in turn determines the rate of pacemaker activity. Ivabradine does not decrease myocardial contractility or affect the cardiac conduction system or ventricular repolarization. In contrast to β-blockers, no rebound effects with drug cessation or pharmacological tolerance with long-term use have been observed following treatment with Ivabradine (DiFrancesco and Camm, 2004).

Because of the negative inotropic effect and effect on atrioventricular conduction, which is amplified in the presence of β-blocker; the first rate lowering line of treatment in this study, especially in patients with left ventricular dysfunction, HR lowering calcium channel antagonists (nondihydropyridine calcium channel antagonists) were not used in this study. Other classes' calcium channel antagonists used only as adjunctive line to the other antihypertensive drugs only.

We also demonstrate that the frequency of angina pectoris attacks and the use of sublingual nitrate therapy had been significantly reduced, $P < 0.001$ for both and the highest significant reduction were observed with group-I.

In concordance with this result, Koster et al., 2009, in which 4954 patients with stable angina pectoris received Ivabradine either alone or in combination with β-blocker were followed for 4 months, demonstrated that angina pectoris attacks were reduced from 2.4 ± 3.1 to 0.4 ± 1.5 per week ($P < 0.0001$) and consumption of short acting nitrates was reduced from 3.3 ± 4.4 to 0.6 ± 1.6 per week ($P < 0.0001$).

In addition, The Coronary Artery Surgery Study (CASS) registry, in which 25,000 patients were followed for 15 years, found that the overall and cardiovascular mortality and cardiovascular morbidity and hospitalizations were increased with increasing heart rate (Diaz et al., 2005).

Also, other studies in post myocardial infarction and heart failure patients have demonstrated clear benefits of treatment with HR lowering drugs with regard to morbidity and mortality (Kjekshus, 1986, The Cardiac Insufficiency Bisoprolol Study II CIBIS-II, 1999; Gullestad et al., 2005; Borer et al., 2003; Tardif et al., 2005).

Stable angina is secondary to increased metabolic demands in the presence of significant coronary artery stenosis. The detrimental effect of a HR increase may be related to several mechanisms, including an increase in oxygen consumption and the workload of the heart, precipitating ischemia and thereby amplifying the risk of a cardiac event. Most ischemia during daily life is associated with significant increases in HR. Also, evidence suggests that tachycardia is associated with increased sympathetic activity and reduced vagal activity. Animal studies show that high heart rates promote atherogenesis, and that this process may be slowed by HR reduction, achieved with surgical ablation of the sinoatrial node. There is also a relationship between mean HR and the genesis of premature ventricular contractions, which is characterized by an increase in the number of tachycardia-enhanced arrhythmias. In addition, increased sympathetic activity and low vagal tone may reduce the threshold for ventricular fibrillation. A fast HR is also associated with coronary plaque disruption (Purcell, 1999; Heidland and Strauer, 2001).

It has also recently been shown that increased HR (and reduced HR variability) are associated with raised C-reactive protein concentration and white cell count, in healthy middle-aged subjects. This subclinical inflammation, coupled with an autonomic imbalance, may be closely linked to atherosclerotic plaque disruption and increased mortality risk (Sajadieh et al., 2004; Purcell, 1999; Heidland and Strauer, 2001).

Conversely, HR reduction in ischemia directly reduces myocardial oxygen demand; prolongation of diastole, caused by a reduction in HR, may increase perfusion to injured myocardium, particularly to the subendocardium, preventing plaque rupture, protecting the ischemic myocardium, and maintaining cardiac contractility (Heidland and Strauer, 2001).

We also demonstrated that, exercise tolerance assessed by exercise treadmill test showed a statistically significant increase in the time to 1 mm ST-segment depression after 4 months of anti-ischemic treatment including rate control drugs and the degree of improvement was significantly higher for group-I than that of group-II. Also, ejection fraction showed a statistically significant increase after 4 months of treatment. The degree of increase was non significantly higher for group-I than that of group-II.

These observations are in agreement with a randomized, double blind study, International Trial of Treatment of the anti-anginal with Ivabradine compaired to atenolol (INTIATIVE), which compared Ivabradine with atenolol over 4 months in 939 patients with stable angina pectoris and documented coronary artery disease. Patients received either Ivabradine 5 mg bid for 4 weeks, increased to 7.5 mg bid for a further 3 months, or atenolol 50 mg daily for 4 weeks, increased to 100 mg daily for a further 3 months. At 4 months, total exercise duration on a treadmill ETT, at lowest treatment activity, increased by 86 s with Ivabradine 7.5 mg and 78 s with atenolol 100 mg (Tardif et al., 2005).

7. Conclusion

Heart rate reduction is clinically feasible and can effectively improve quality of life in patients with stable coronary heart disease. Thus, it seems sensible to reduce both heart rate and the demands for myocardial oxygen consumption in patients with coronary artery disease.

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